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Clinical Outcome and Prognostic Factors for Ischaemic Ulcers Treated with PTA in Lower Limbs

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Objective: to analyse the clinical outcome of patients with ischaemic ulcers (Fontaine stage IV) undergoing percutaneous transluminal angioplasty (PTA).

Methods and design: retrospective cohort study of 40 patients (21 males) treated between January 1998 and December 1998. Cardiovascular risk factors, co-morbid, baseline laboratory, angiographic data and technical success were recorded. Patients were followed for a median of 20 (inter quartile range [IQR] 8–26) months.

Results: cumulative ulcer healing rates at 3, 6, 12, and 24 months were 15, 40, 54 and 81%, respectively. The median time to healing was 5 (IQR 2–7) months. Cumulative restenosis at 1, 3, 6 and 12 months was 3, 10, 29 and 52%, respectively. Nine patients (22%) suffered ulcer reappearance. Lipoprotein (a) serum levels >30 mg/dl (HR 0.2, 95% CI 0.05–1.0, $p = 0.05$) and diabetes mellitus (HR 0.2, 95% CI 0.5–0.7, $p = 0.01$) were associated with delayed ulcer healing.

Conclusion: PTA leads to ulcer healing in the majority of patients. Elevated lipoprotein (a) levels >30 mg/dl and diabetes mellitus are independently associated with ulcer persistence.

Key Words: Peripheral arterial disease; Lipoprotein(a); Diabetes mellitus.

Introduction

Symptomatic peripheral artery disease (PAD) affects 3–6% of all patients over 60 years of age.^{1–3} Critical limb ischaemia occurs in approximately 5% of these patients within 5 years from initial symptoms and causes considerable morbidity and costs.^{1,4–8} Persistent ulceration, osteomyelitis or gangrene frequently necessitate major surgical revision or amputation.^{9–11} Multi-segmental vessel lesions and extensive involvement of crural arteries characterise the atherosclerotic vascular changes in these patients.^{1,12} Patients with diabetes mellitus have a two to threefold increased risk for development of ischaemic ulcers compared to non-diabetics.^{1,13,14}

Chronic critical limb ischaemia may be treated conservatively, surgically or by percutaneous endovascular procedures.^{15–23} The major disadvantage of the surgery is the invasiveness of the procedure and the peri-operative risk.¹ However, only approximately 20–30% of patients with affected crural arteries have

anatomy favourable for percutaneous transluminal angioplasty.^{24–26} Furthermore, the rate of restenosis after endovascular treatment is high. Therefore, PTA has been considered primarily for patients with limited disease.^{24,26,27} Data concerning endovascular treatment of patients with extensive multi-segmental PAD and critical limb ischaemia are limited.

The aim of the study was to analyse the clinical outcome of patients with extensive multi-segmental peripheral artery disease and ischaemic ulcers (Fontaine stage IV) undergoing percutaneous transluminal angioplasty (PTA) in the femoropopliteal region. Primary endpoint was ulcer healing. Furthermore, prognostic parameters for ulcer persistence were assessed in these patients.

Material and Methods

Study design

This was a retrospective study of all patients with multi-segment PAD and ischaemic ulcers (Fontaine stage IV) who underwent femoropopliteal PTA between January 1998 and December 1998. Patients

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who were treated additionally with PTA for crural and iliac disease were also included.

The study was performed according to the Declaration of Helsinki.

Definitions

Hypercholesterolaemia was defined as baseline serum cholesterol above 5.2 mmol/l or serum LDL above 3.4 mmol/l. Diabetes mellitus was classified in patients with a history of diabetes and in patients with a HbA1c level above 6.5%. Arterial hypertension was diagnosed according to the WHO criteria. Patients who were smoking >3 cigarettes daily, were regarded as current smokers.

Poor run off was defined as either occlusion or significant stenosis of the femoral or popliteal artery distal to the treated segment and/or in patients with occlusions of at least two crural arteries. An occlusion/stenosis length up to 5 cm was defined as short lesion, otherwise as a long lesion. Trophic ischaemic lesions with a diameter below 4 cm and a depth below 0.5 cm were classified as minor ulceration, all other ulcers were defined major ulceration. Amputation of a toe or mesh-graft implantation was classified as minor surgery. Major surgery was defined as bypass-implantation or any other amputation.

Patient data

Demographic and interventional data were recorded retrospectively by systematic review of patients charts and review of the PTA registry. Patients age, sex, atherothrombotic risk factors and cardiovascular co-morbidities were documented. Routine laboratory parameters at admission included complete blood count, leucocytes, serum creatinin, C-reactive protein, HbA1c, fibrinogen, lipoprotein (a), total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides and uric acid. Pre- and postinterventional ankle-brachial index was recorded. Colour coded duplex examinations were performed at baseline and 24 h after the intervention (5 MHz, linear array colour probe [model XP 10; Acuson, Mountain View, CA, U.S.A.]) and if necessary at any other follow up visit. The maximum peak systolic velocity (PSV) in the dilated region was determined and compared to the PSV in the preceding normal segment. A focal increase in the PSV of at least 140% (corresponding to a peak velocity ratio [PVR] of ≥ 2.4) was considered indicative of a stenosis of

greater than 50% at that site. Peri-interventionally all patients received twice daily intravenous Prostaglandin E₁ (40 µg Alprostadil, Prostavasin, Gebro Fieberbrunn, Austria) during a time interval of 10–14 days. All patients received a long-term antiplatelet therapy with acetylsalicylic acid 100 mg once daily.

Follow up

After PTA, all patients were invited routinely at 1, 3, 6 and 12 months for follow-up investigations and thereafter annually. Follow-up investigations consisted of oscillography, Doppler measurements and clinical investigation. Patients with new onset of claudication or increase of complaint as well as patients with significant reduction of ankle-brachial index (deterioration by at least 0.15 from the maximum postprocedural level) were further evaluated with colour coded duplex sonography.^{28–30} Patients with incompressible arteries and unjudgeable ABI due to mediasclerosis underwent oscillography and measurement of arterial toe-pressure to stage the disease. Non-compressibility was assessed by missing or hardly detectable pressure decrease during proximal compression. In these patients arterial toe pressure was used for calculation of the ABI. Patients were followed until ulcer healing or, in case of ulcer persistence, until the end of the study period. Re-occurrence of ulcers is not included in the life table analysis.

All patients showed a multi-segmental disease with obstructive target lesions in the femoro-popliteal segment. Thirty-two patients had two patent arteries and 8 patients showed one patent crural artery, no patient had three patent arteries in the crural section. However, patients with persistent ulceration were followed in two weeks intervals at the outpatient ward of the department until ulcer healing. Restenosis was defined as a 50% diameter reduction at the dilated segment. The rate of restenosis was assessed by colour coded duplex sonography and follow up angiograms, if available.

Statistical methods

Continuous data are presented as the median and interquartile range (range from the 25th to the 75th percentile). Percentages were calculated for dichotomous variables. The Wilcoxon test was used for comparison of continues, paired variables. The course of ulcer healing after PTA was assessed using Kaplan-Meier curves and life table analysis. The Log Rank test was used for univariate comparison

of baseline data. A multivariate Cox proportional hazard model was applied to assess independent predictors for ulcer healing and to adjust for confounding factors. All *p*-values are two sided, a *p*-value < 0.05 was accepted as statistically significant. Calculations were performed using SPSS for Windows (Version 10.0).

Results

Forty eligible patients were treated within the one year period, all patients were included in the study. The median age was 74 years (IQR 65–80). Demographic data shown in Table 1.

Median diameter of the ischaemic ulcers was 2 cm (IQR 1–4). Minor ulceration was found in 25 patients (62%), major ulceration was observed in 15 patients (38%). The majority of ulcers was found located at the toes (*n* = 25, 62%). Ulceration persisted for at least 3 months prior to intervention.

Additional to endovascular procedures in the femoro-popliteal segment a PTA in crural arteries was performed in 14 patients (37%). No stent implantation was performed in the crural arteries. Additional PTA and stent implantation in the iliac artery was performed in 3 patients (7%).

The median grade of stenosis of the treated femoro-popliteal segment was 80% (IQR 74–100). The median length of the treated occlusion/stenosis was 5 cm (IQR 4–7). Complete occlusion in the femoropopliteal segment was detected in 11 patients. The median pre-interventional ankle-brachial index (ABI) was 0.32 (0.23–0.38). Not compressible arteries due to mediasclerosis were found in 21 patients (53%).

Peri-interventional complications occurred in 7 patients (three vessel-dissections and four post-interventional bleedings). All bleeding complications were treated conventionally by manual compression. The ABI improved significantly post-interventionally to median 0.7 (IQR 0.51–0.76) (*p* < 0.0001). After PTA, residual stenosis (>30%) at the dilated segment was found in 25 cases (62%) 24 h after PTA assessed by colour coded duplex sonography.

Table 1. Multivariate Cox proportional hazard model assessing the risk for ulcer healing within the median observation period of 20 months (IQR 8–26).

	HR	95% CI	<i>p</i> -value
Age (1 year increments)	1.0	0.9–1.0	0.5
Male sex	1.1	0.5–2.7	0.8
Lipoprotein(a) >30 mg/dl	0.2	0.05–1.0	0.05
Diabetes mellitus	0.2	0.5–0.7	0.01

Follow up

The median follow-up interval was 20 months (IQR 8–26). None of the patients died or were lost during the follow-up period. Minor surgery was performed in 9 patients (22%) and 4 patients (10%) underwent major surgery. Healing of trophic lesions within the follow-up period was found in 24 patients (60%). The median healing interval was 5 months (IQR 2–7) (Fig. 1). Cumulative healing rates at 3, 6, 12, and 24 months were 15, 40, 54 and 81%, respectively. A re-appearance of ulcers was found in 9 patients (22%).

Univariate comparison of risk factors for ulcer persistence showed that patients with diabetes had a significantly reduced healing rate (Log Rank *p* = 0.03). Patients with elevated lipoprotein(a) >30 mg/dl had a trend towards a reduced healing rate (Log rank *p* = 0.1). Length of the dilated lesion, grade of stenosis, residual stenosis at the dilated segment, number of crural vessels and procedure complications were not associated with ulcer healing in this patient series. Patients age, gender, atherosclerotic co-morbidities (coronary artery disease, carotid artery stenosis) and the atherothrombotic risk factors smoking, arterial hypertension and hyperlipidaemia showed also no association with ulcer healing (Table 2). In the present patient series lipoprotein(a) levels were not associated with restenosis (*p* = 0.8). A multivariate Cox proportional hazard model was applied to assess the independent effect of vascular risk factors on ulcer healing and to adjust for patients age and sex. Diabetes mellitus and elevated levels of lipoprotein(a) >30 mg/dl were inversely

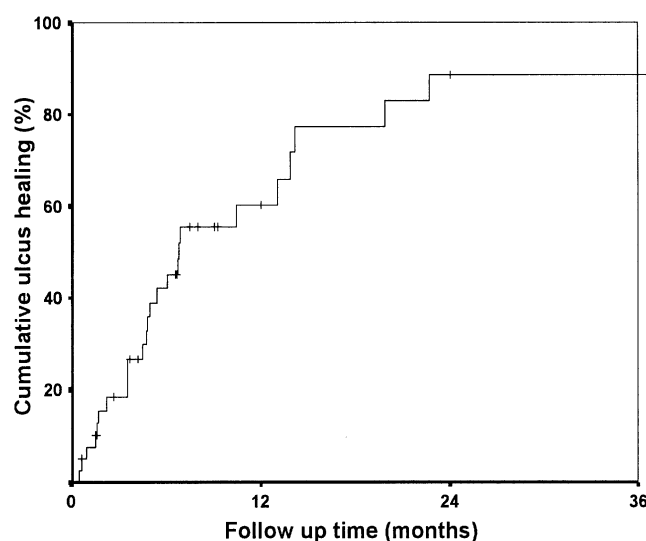


Fig. 1. Healing of ischaemic ulceration in patients with multi-segmental peripheral artery disease Fontaine IV after endovascular revascularisation.

Table 2. Demographic data of 40 patients with ischaemic ulceration of the lower limb and endovascular treatment of the femoro-popliteal segment.

	Patients with ulcer healing (n = 24, 60%)	Patients without ulcer healing (n = 16, 40%)	p-value
Female sex	11 (28%)	8 (20%)	0.7
Arterial hypertension	16 (43%)	6 (15%)	0.2
Diabetes mellitus	20 (50%)	12 (30%)	1.0
Habitual smokers	11 (28%)	6 (15%)	1.0
Coronary heart disease	15 (38%)	5 (13%)	0.2
Carotid artery plaques/stenosis*	6 (15%)	6 (15%)	0.3
Hyperlipidaemia	11 (28%)	4 (10%)	0.3

* $\geq 25\%$ luminal narrowing.

Table 3. Life table calculated by the Kaplan–Meier method.

Time interval	Patients at risk	Cumulative restenosis rate	Standard error
1 month	40	1 (3%)	0.025
3 months	34	4 (10%)	0.079
6 months	26	11 (29%)	0.190
12 months	16	21 (52%)	0.136

associated with ulcer healing, i.e. increased risk of ulcer persistence (Table 1).

Cumulative rates of restenosis after 1, 3, 6 and 12 months were 3, 10, 29 and 52%, respectively (Table 3). A re-intervention after a median interval of 5 months (IQR 3–8) was performed in 15 patients (37%). The need for re-intervention was not associated with altered healing rates (Log rank $p=0.5$), since all reintervention successfully restored vessel patency. Similarly, primary restenosis ($n=21/40$) showed no significant association with ulcer healing during the observation period. Similarly, primary restenosis ($n=21/40$) showed no significant association with ulcer healing, since reinterventions were performed in the majority of these patients ($n=15/21$) to restore vessel patency. Similarly, primary restenosis ($n=21/40$) showed no significant association with ulcer healing during the observation period.

Discussion

A majority of patients with multi-segmental peripheral artery disease and chronic critical limb ischaemia can be successfully treated with PTA. Ischaemic ulcers in patients with diabetes mellitus and elevated serum levels of lipoprotein(a) >30 mg/dl showed a lower rate of healing.

All patients in this study were elderly and frequently suffered several co-morbidities, but remarkably none

of these patients died within the follow up period. However, in many cases surgical revascularisation would not have been feasible with acceptable peri-operative risk. In particular, costly crural reconstructions frequently would have been necessary, as crural arteries were affected in all patients. PTA is less invasive and risky. However, technical success in these patients often remains unsatisfactory, which is indicated by the high proportion of patients with residual stenosis at the dilated segment 24 h after the intervention. Nevertheless, even partial restoration of distal blood supply after PTA may initiate ulcer healing. The median healing interval of 5 months after successful revascularisation compares well to the literature.^{27,31,32} Remarkably, even in this series of patients with severe vessel morphology treatment success in terms of ulcer healing was observed frequently.

The finding that diabetes was a risk factor for ulcer persistence is in line with published data.^{33–35} Arterial occlusive disease in diabetics is characterised by macroangiopathy frequently affecting the crural arteries extensively³⁶ as well as microangiopathy. Macroangiopathy may be treated successfully by means of PTA restoring blood flow in the large arteries in the proximal crural segments. Persistent haemodynamic impairment in the distal crural arteries in diabetic patients leads to significantly reduced ulcer healing rates compared to patients with isolated non-diabetic macroangiopathy.^{28,37,38}

Lower patency rates were found previously in patients with elevated levels of lipoprotein(a)³⁹ and thus may cause reduced ulcer healing, however in the present patient series no association between lipoprotein(a) levels and restenosis were observed. Furthermore, increased lipoprotein(a) serum levels are associated with endothelial dysfunction and vasoconstriction in patients with atherosclerosis.^{40–42} This may also contribute to a reduced compensatory haemodynamic reserve and increased risk for ulcer persistence.

Primary restenosis was not associated with ulcer healing. This may be explained by the fact, that the majority of these patients successfully underwent reinterventions and sustained vessel patency was achieved in this patients during the observation period.

Limitations

The retrospective study design implies some limitations. However, due to a strict peri-intervention protocol at our department and strict follow-up intervals,

data were almost complete in all patients and no patient had to be excluded from the analysis. Patients were identified by our PTA registry, which records all endovascular interventions. Due to the retrospective study design we were not able to completely clarify the pathogenesis of ulcers, particularly, segregation between neuropathic and ischaemic pathogenesis of the ulcers is difficult. However, extensive arterial obstructions were found in all patients implicating that ischaemia played a pivotal role in the pathogenesis of these ulcers. The median ABI of 0.32 referred just to patients without media calcification, including all patients the median ABI was 0.4 (including patients with media sclerosis). This indicates that patients with media sclerosis also had reduced ABI and haemodynamical relevant atherosclerotic lesions.

Diabetes mellitus is an established risk factor for peripheral artery disease, lower limb ulceration.^{33–35} In the present patient series a high incidence of diabetes was found (80%) and the finding that diabetes is a risk factor for ulcer persistence is in line with published data.^{33–35}

Due to the combination of PTA and PGE₁ it is in fact impossible to exactly separate the treatment effects of PTA and PGE₁. Therefore our conclusion on lipoprotein(a) and ulcer healing refer to the combined treatment of PTA and PGE₁, which we considered superior to PTA alone.

Conclusion

Peripheral percutaneous transluminal angioplasty may restore sufficient distal blood flow for ulcer healing in selected patients with severe multi-segmental vessel lesions. Diabetes mellitus and elevated lipoprotein(a) levels >30 mg/dl were independently associated with an increased risk for ulcer persistence.

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